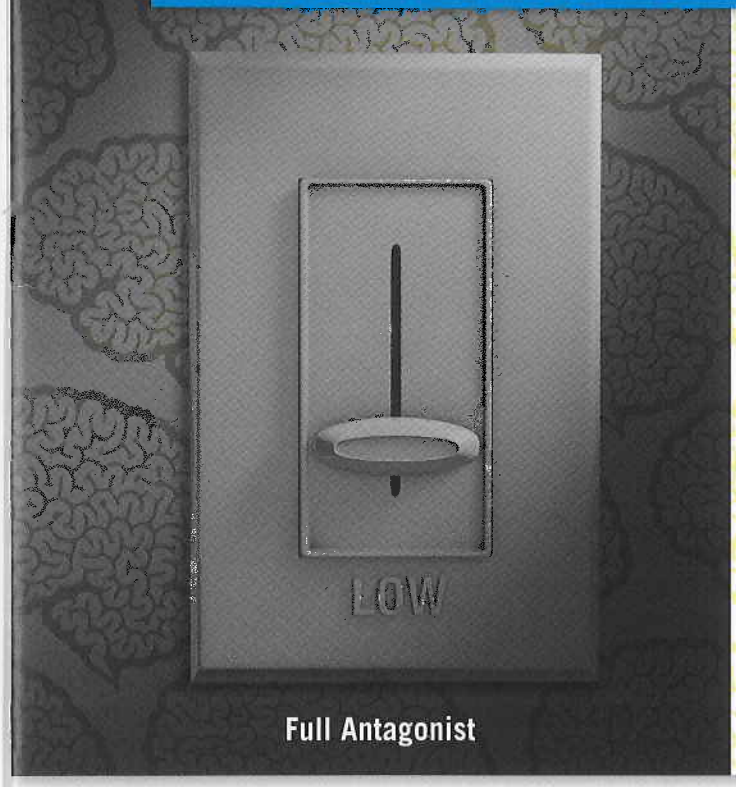
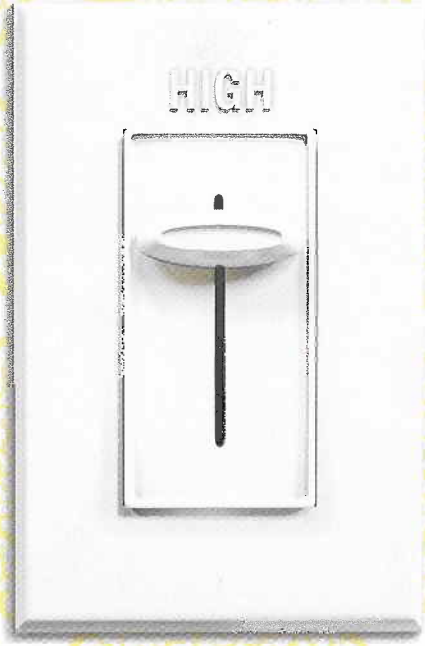
ABILIFY® (aripiprazole) is the only commercially available partial agonist that modulates both synaptic dopamine and serotonin*



Full Antagonist



Full Agonist

***Although the mechanism of action of ABILIFY® (aripiprazole) is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D_2 and serotonin $5HT_{1A}$ receptors, and antagonist activity at the serotonin $5HT_{2A}$ receptors. Actions at receptors other than D_2, $5\text{-}HT_{1A}$, and $5\text{-}HT_{2A}$ may explain some of the other clinical effects of aripiprazole (eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors).**

Indication

ABILIFY is indicated for:

- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Acute and maintenance treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate in adults

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNINGS**, and INDICATIONS, for ABILIFY on pages 4 and 5.

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

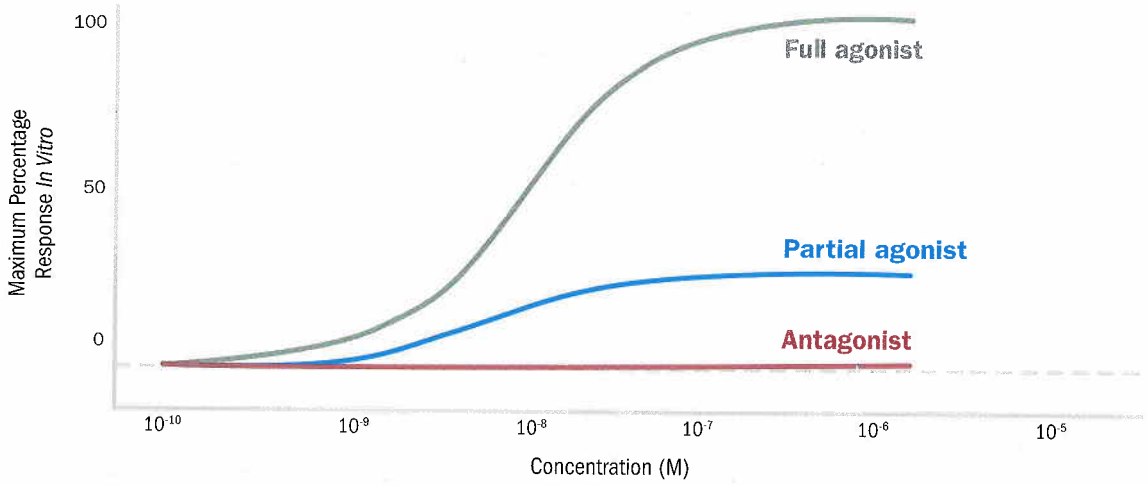
ABILIFY® (aripiprazole) is a partial agonist at both dopamine and serotonin receptors*

Receptor Activity†‡

Receptor System	Dopamine	Serotonin
Neuroreceptor Subtype/Action	D_2 partial agonist D_3 partial agonist	5-HT_{1A} partial agonist 5-HT_{2A} antagonist

***Although the mechanism of action of ABILIFY is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D_2 and serotonin 5HT_{1A} receptors, and antagonist activity at the serotonin 5HT_{2A} receptors.**
†Based on preclinical data.
‡Data with cloned human receptors.

Theoretical action of partial agonist compared to full agonist and antagonist[1]



A partial agonist may have the same potency as a full agonist, but at a lower maximal level of response.

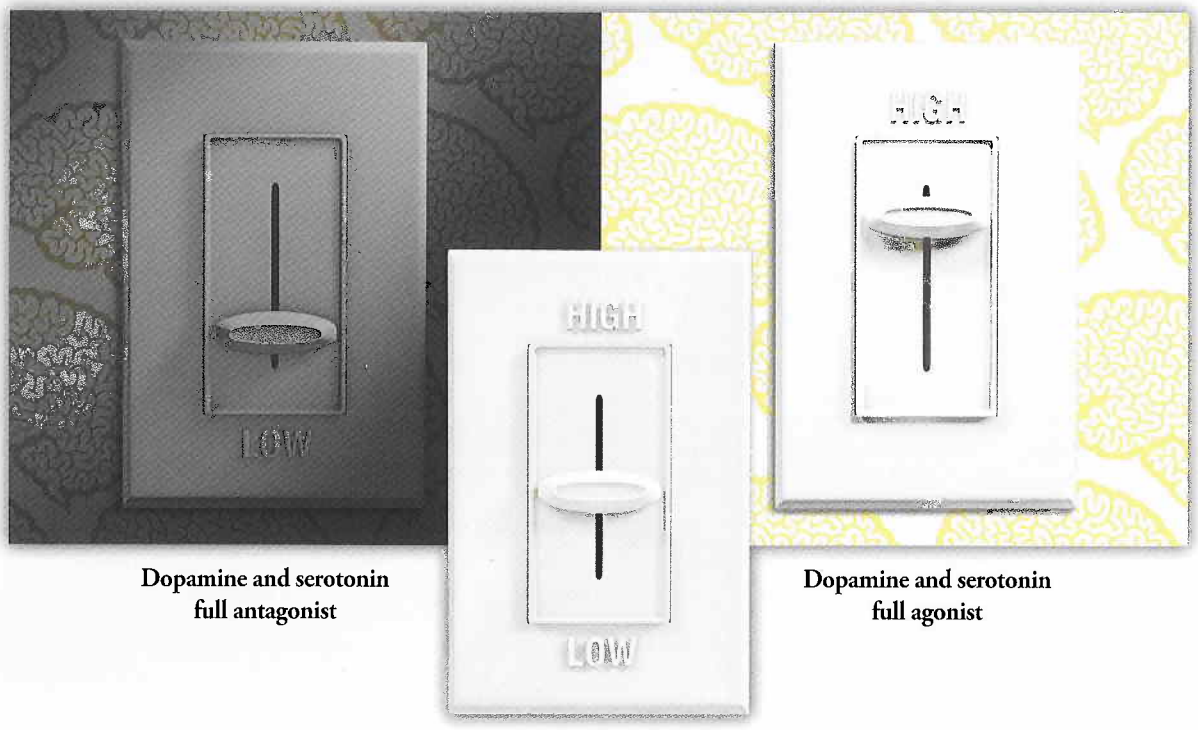
Indication

ABILIFY is indicated for use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy.

Contraindication

Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Modulating dopaminergic and serotonergic activity sets ABILIFY® (aripiprazole) apart[2]*



Dopamine and serotonin full antagonist

Dopamine and serotonin full agonist

Help modulate dopamine and serotonin activity with ABILIFY

ABILIFY is thought to partially activate dopamine and serotonin receptors, thereby modulating neuronal activity in both hypoactive and hyperactive environments[3]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Important Warning and Precaution for Cerebrovascular Adverse Events, Including Stroke

Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNINGS**, and INDICATIONS, for ABILIFY on pages 4 and 5.

ABILIFY® (aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

INDICATIONS

ABILIFY is indicated for:

- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate in adults
- Maintenance treatment of Bipolar I Disorder, both as monotherapy and as an adjunct to lithium or valproate in adults

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindication – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

- **Cerebrovascular Adverse Events, Including Stroke** – Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Neuroleptic Malignant Syndrome (NMS)** – As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems
- **Tardive Dyskinesia (TD)** – The risk of developing TD and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn
- **Metabolic Changes** – Atypical antipsychotic drugs have been associated with metabolic changes that include:
  - **Hyperglycemia/Diabetes Mellitus** – Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug
  - **Dyslipidemia** – Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between ABILIFY- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs
  - **Weight Gain** – Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended

Orthostatic Hypotension – ABILIFY may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole) *(continued)*

Leukopenia, Neutropenia, and Agranulocytosis – Leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotics, including ABILIFY. Patients with history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions – As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold (eg, Alzheimer's dementia).

Potential for Cognitive and Motor Impairment – Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Body Temperature Regulation – Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Suicide – The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Dysphagia – Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder. If a strong CYP3A4 inhibitor and strong CYP2D6 inhibitor are coadministered or a known CYP2D6 poor metabolizer is receiving a concomitant strong CYP3A4 inhibitor, the ABILIFY dose should be reduced to one-quarter (25%) of the usual dose.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)
- Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs 4%), sedation (8% vs 3%), tremor (6% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%)
- Adult patients (adjunctive therapy with lithium or valproate) with Bipolar Mania: akathisia (19% vs 5%), insomnia (8% vs 4%), and extrapyramidal disorder (5% vs 1%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Non-Teratogenic Effects – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These complications have varied in severity; from being self-limited to requiring intensive care and prolonged hospitalization. ABILIFY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – ABILIFY is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see accompanying FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, for ABILIFY in pocket.

1. Green B. Focus on aripiprazole. *Curr Med Res Opin.* 2004;20(2):207-213. Review.
2. Fleischhacker WW. Aripiprazole. *Expert Opin Pharmacother.* 2005;6(12):2091-2101.
3. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. *J Clin Psychiatry.* 2001;62(12):923-924.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.

ABILIFY (aripiprazole) TABLETS and ORAL SOLUTION 1 mg/mL

Otsuka Otsuka America Pharmaceutical, Inc.

January 2014 03US13EP0314 Printed in USA

Unique pharmacology sets ABILIFY® (aripiprazole) apart*

ABILIFY

- Is thought to increase neuronal activity in hypoactive conditions[3]
- Is thought to decrease neuronal activity in hyperactive conditions[3]
- Has a high affinity for both dopamine and serotonin receptors
- Functions as a partial agonist at the dopamine D_2, D_3 and the serotonin 5-HT_{1A} receptors, and as an antagonist at the serotonin 5-HT_{2A} receptor

The mean elimination half-lives of aripiprazole and dehydro-aripiprazole are 75 hours and 94 hours, respectively.

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